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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
RISHI, ANJUM I

ART UNIT	PAPER NUMBER
1632	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/864,364	SONE ET AL.	
	Examiner	Art Unit	
	Anjum I Rishi	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

The abstract of the disclosure is objected to because the abstract is more than one paragraph. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 25 provides for the use of non-human bone metastasis model animal for determining the effect of a test substance on bone metastasis, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 25 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7,10-21 and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a SCID or nude mouse exhibiting bone metastasis of small cell lung carcinoma cell line SBC-5 tumor cells, wherein the tumor cells are introduced by peripheral administration, and a method for using the mouse for evaluating efficiencies of treatment against bone metastasis, does not reasonably provide enablement for producing any and all non-human animals exhibiting bone metastasis of any and all tumor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification discloses a non-human bone metastasis model animal, wherein the tumor cells are introduced by peripheral administration, wherein the tumor cells are preferably derived from human lung small cell carcinoma or breast cancer. Further, the specification discloses that the animal is an immunodeficient mouse or SCID mouse. In addition, the tumor bone metastasis model disclosed in the specification includes a step of inactivating or reducing or depleting NK cells and further administering anti-IL-2 receptor antibody to the animal, wherein the antibody is anti-IL- receptor beta-chain antibody. Further, the claims are drawn to a method for evaluating efficiency of treatment against bone metastasis by applying a treatment to the animal model and

comparing the size and/or extent of bone metastasis and /or symptoms with control animal.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The examples in the specification disclose that eight different human lung cancer cell line were injected into NK-cell depleted SCID mice through tail vein. Only one cell line SBC-5 developed metastatic colonies to the bone as well as other organs. Applicant's results showed that number of bone and visceral metastasis depended on number of cells that were injected. Based on their results they injected $1x\ 10^6$ SBC-5 cells in subsequent experiments. Further experiments showed that SBC-5 cells secreted more than 10 times higher levels of PTHrP compared to other cell lines. They conclude from their experiments that there is a direct correlation of bone metastasis and

level of serum calcium and PTHrP. In addition they conclude that there is no correlation between the expression of cytokines and formation of bone metastasis.

The working examples are not sufficient to support the breadth of the claims, as the claims encompass efficacy of the instantly claimed invention using any and all tumor cells. The claims are broadly drawn to the use of a non-human mammal as a model system for bone metastasis. The specification does not provide sufficient guidance for the use of any and all animals or any and all tumor cells to make the disclosed model of bone metastasis. The specifications only working examples disclose the formation of bone tumors in SCID mice, while the claims recite any non-human animal in which tumor cells are introduced by peripheral administration (claim 1). In addition, the specification fails to address the issue of graft versus host disease and immune rejection in non-autologous tumor grafts. The specification reads on the installation of human lung tumor cells into a mammal. In the absence of substantial immunodeficiency, foreign tissue is rapidly rejected by the host mammal's immune system. Rejection is largely mediated by complement, cytotoxic T cells, and antibody-dependent cellular cytotoxicity. Antibody mediated rejection of tissue is particularly strong in the case of discordant xenogeneic tissue due to the presence of preformed anti-xenogeneic antibodies in the host mammal. Xenogeneic transplantation can be sub-divided into two categories, concordant and discordant, depending on the degree of genetic disparity between the donor and host species. Whereas transplantation between a rat and a mouse is considered concordant, transplantation between a mouse and a human, or a pig and a human is considered discordant. The host immune

response to a discordant graft is significantly stronger than that observed to a concordant graft due primarily to the increased frequency of natural preformed antibodies in the host that recognize discordant antigens and cause hyper acute rejection of the foreign tissue. Naturally occurring xenoantibodies can mediate hyper acute rejection (HAR) of xenogeneic tissue in as little as 2 hours (Kaufman et al., (1995), Annul. Rev. Immunol., Vol. 13, 339-367). Prevention of rejection in xenotransplants requires inhibition or suppression of multiple components of both the immune and inflammatory responses. According to Kaufman et al., " In experimental and clinical protocols in which immunosuppressive agents ... were administered to recipients of xenografts, vigorous rejection occurred, even when profoundly immunosuppressive combinations of agents were utilized, " (Kaufman et al. (1995), *supra*, page 347). Hence the specification is only limited to practice of present invention in immunodeficient animals to support the foreign tumor cells.

The applicants further claim practice of the current invention in immunodeficient mouse (claim 8) or a non-human animal having reduced immunity (claim 10) but the specification does not provide any guidance for the practice of the present invention in other forms of immunocompromised mice encompassed by the claims or for the level or type of immunodeficiency that will allow any tumor cells to metastasize to the bone for example: genetically immunodeficient mice versus radiation/chemically induced immunodeficient mice.

In one embodiment, the specification discloses inactivating NK cell function (p.9) by antibody or Tm beta 1 treatment or X-ray irradiation to the whole body of the mouse.

It discloses using the method in described in Japanese patent No. 3040451, but the applicants did not provide any copies and does not identify the essential teaching by page and line number. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In addition, the specification teaches the use of any tumor cell to make the bone metastasis model. How ever, specification discloses that the applicants were not successful in creating such a model with all the eight different tumor cell lines they used except for the small cell lung carcinoma line SBC-5 (p.14). The specification does not teach what characteristics of a tumor cell will lead it to metastasize to bone. The observation of bone metastasis seems to be unique to the human lung cancer SBC-5 cell line.

Further, the specification does not disclose what level of X-rays to use which correlate with inactivating NK cell function. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery,

not to find out how to use it for themselves. see In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Thus, due to the lack of guidance provided in the specification as to the characteristics of tumor cells which are capable of generating bone metastases in different animals which are recited in the specification, the lack of guidance regarding the level of immunodeficiency which is required to allow the growth and metastases of foreign tumors in the instant models, and the breadth of the claims; it would have required undue experimentation to practice the scope of instant invention and the skilled artisan would not have predicted success in producing any and all non-human animals except SCID or nude mice exhibiting bone metastasis of any tumor cell, except the human SBC-5 cell line.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-10, 12 and 19-25 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by US patent number 5,643,551, hereafter refered to as Namikawa et al.

Claims are drawn to a non-human bone metastasis model animal, wherein the tumor cells are introduced by peripheral administration, wherein the tumor cells are derived from human lung small cell carcinoma. Further, the animal comprising the bone metastasis model is an immunodeficient mouse or SCID mouse.. Further, the claims are drawn to use of the animal model and a method for evaluating efficiency of treatment against bone metastasis by applying a treatment to the animal model and comparing the size and/or extent of bone metastasis and /or symptoms with control animal.

Namikawa et al teaches a non-human mammal (See abstract, line 3), wherein the non-human mammal is a SCID mouse (column 2, line 39 and line 44) in which tumor cells are introduced by peripheral administration including intravenous, intraperitoneal or subcutaneous injection (column 3, line 12-13 and column 4, line 29), and wherein the tumor cells used comprise lung or small cell lung carcinoma (SCLC) or breast (column 4, line 14 and line 18) and show an increased ability to migrate to bone marrow and cause tumor growth within (column 15, line38). He also teaches evaluation of treatments against tumor metastasis using the disclosed model (column 2, line 21-26).

Thus by teaching the all the elements of the claims, Namikawa et al. anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2,11,13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over US patent number 5,643,551, hereafter refered to as Namikawa et al. and in view of Yano et al. (1996), International journal of cancer, vol. 67 (2), pages; 211-217 and in view of Mundy et al. (2001 apr.), seminars in Oncology, vol. 28 (2 suppl. 6), pages; 35-44.

Claims are drawn to a non-human animal having reduced immunity exhibiting bone metastasis of tumor cells, wherein the tumor cells are human lung cancer or breast cancer derived cells highly expressing PTHrP and are capable of bone metastasis. Further, introducing the tumor cells by peripheral administration. In addition, the claims include a step to inactivate or reduce or deplete NK cells in the animal by administering anti-IL-2 receptor antibody, wherein the antibody is a mouse anti-IL-2 beta-chain antibody.

Namikawa et al teaches a non-human mammal (See abstract, line 3), wherein the non-human mammal is a SCID mouse (column 2, line 39 and line 44) in which tumor cells are introduced by peripheral administration including intravenous, intraperitoneal or subcutaneous injection(column 3, line 12-13 and column 4, line 29), and wherein the tumor cells used comprise lung or small cell lung carcinoma (SCLC) or breast (column 4, line 14 and line 18) and show an increased ability to migrate to bone marrow and cause tumor growth within (column 15, line38). He also teaches evaluation of treatments against tumor metastasis using the disclosed model (column 2, line 21-26).

Namikawa et al differs from the present invention by not teaching that the tumor bone metastasis model includes a step of inactivating or reducing or depleting NK cells and further administering anti-IL-2 receptor antibody to the animal, wherein the antibody is anti-IL- receptor beta-chain antibody and further is a mouse antibody. He also does not teach that the tumor cells are highly expressing PTHrP.

Yano et al supplements Namikawa et al by teaching administration of anti mouse IL-2 receptor beta chain antibody in SCID mice to deplete NK cells and further provides motivation by suggesting that NK-cell depleted SCID mice may be useful as a model in biological and pre-clinical studies on metastasis of human lung cancer (See abstract).

Mundy et al teaches breast cancer cells expressing high levels of PTHrP (See p.37, line 11-13 and 19-21). He further provides motivation for using tumor cells highly expressing PYHrP for making animal models of bone metastasis " Parathyroid hormone related peptide is secreted by metastatic breast cancer cells in bone in which it acts as a paracrine factor to stimulate osteoclasts." (See page 35, line 10-14).

In view of the motivation provided by Yano et al to deplete NK cells, and motivation provided by Mundy to use tumor cells highly expressing PTHrP for bone metastasis, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the method taught by Namikawa for making an animal model for bone metastasis to include a step of depleting NK cells by administering anti-IL- receptor beta-chain antibody and using tumor cells highly expressing PTHrP, with a reasonable expectation of success.

Conclusi n

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anjum I Rishi whose telephone number is (703) 308-4422. The examiner can normally be reached on M-F (8:30am-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (308) 8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the art unit patent analyst Pinkney Kay whose telephone number is (703) 305-3553.

Anjum Rishi

A.M.S. BECKERLEG
PATENT EXAMINER